AMENDMENTS TO THE SPECIFICATION

Please amend the specification, as follows:

Please replace the Sequence Listing filed July 2, 2004, with the Substitute Sequence Listing filed herewith. The Substitute Sequence Listing corrects an error which occurred in the Supplemental Sequence Listing filed on July 2, 2004. In particular, the amendment corrects the amino acid at position 80 of SEQ ID NOS: 3 and 4 by changing Threonine (Thr) to Tyrosine (Tyr).

Applicants note that the originally filed Sequence Listing on December 12, 2003 included Tyrosine (Tyr) at position 80 in SEQ ID NOS: 3 and 4. Accordingly, this correction does not constitute new matter.

Also, the Sequence Listing presently includes SEQ ID NOS: 5 and 6 which have been added to address the objection of Figure 10 in the Office Action; and SEQ ID NO: 7 which has been added to list -Ala-Ala-Pro-Val, which is a portion of the fluorogenic synthetic substrate Suc(OMe)-Ala-Ala-Pro-Val-MCA which is cited in the specification.

Please replace the paragraph appearing at page 4, lines 12-22, with the following amended paragraph:

Thus, the present invention provides a blood coagulation factor IX-activating protein derived from a mammal, which has an amino acid sequence of ~~SEQ ID NO:4~~ SEQ ID NO:4 and has the following properties:

(1) the protein acts on blood coagulation factor IX to activate said factor;

(2) the activity of the protein is inhibited in the presence of an α1-protease inhibitor or soybean trypsin inhibitor;

(3) the protein is present in erythrocyte membrane;

(4) the protein has a molecular weight of approximately ~~29~~ 25.7 kDa as measured by SDS-PAGE.

Please replace the paragraph on page 6, lines 13-22, with the following amended paragraph:

According to still another aspect of the present invention, there is provided a method for screening an inhibitor for the blood coagulation factor IX-activating protein according to the present invention, wherein said the blood coagulation factor IX-activating protein is used. Preferably, a fluorogenic synthetic substrate, the blood coagulation factor IX-activating protein according to the present invention and a candidate inhibitor are mixed and incubated, and then the fluorescence intensity is measured. Further preferably, the fluorogenic synthetic substrate is Suc(OMe)-Ala-Ala-Pro-Val-MCA (SEQ ID NO:7).

Please replace the paragraph on page 9, lines 5-14, with the following amended paragraph:

The blood coagulation factor IX-activating protein derived from a mammal of the present invention[[,]] is characterized by the following properties:

(1) the protein acts on blood coagulation factor IX to activate said factor;

(2) the activity of the protein is inhibited in the presence of an α1-protease inhibitor or soybean trypsin inhibitor;

(3) the protein is present in erythrocyte membrane;

(4) the protein has a molecular weight of approximately ~~29~~ 25.7 kDa as measured by SDS-PAGE.

Please replace the paragraph on page 9, lines 15-16, with the following amended paragraph:

The blood coagulation factor IX-activating protein of the present invention has an amino acid sequence of ~~SEQ ID NO:4~~ SEQ ID NO:4.

Please replace the paragraph on page 10, lines 21-23, with the following amended paragraph:

The blood coagulation factor IX-activating protein of the present invention has a molecular weight of approximately ~~29~~ 25.7 kDa as measured by SDS-PAGE.

Please replace the paragraph linking page 21 at line 31 to page 22 at line 14 with the following amended paragraph:

By using the ~~the~~ blood coagulation factor IX-activating protein according to the present invention, an inhibitor for said blood coagulation factor IX-activating protein can be screened. Such screening is also included in the scope of the present invention. The screening can be carried out, for example, by mixing and incubating a fluorogenic synthetic substrate, the blood coagulation factor IX-activating protein according to the

present invention and a candidate inhibitor, and then measuring the fluorescence intensity. As the fluorogenic synthetic substrate, for example, Suc(OMe)-Ala-Ala-Pro-Val-MCA (SEQ ID NO:7) can be used. Examples of the candidate inhibitor include, but not limited thereto, low molecular weight synthetic compounds, extracts from naturally-occurring substances, compound library, phage display library, or combinatorial library. A process for constructing a compound library is known to persons skilled in the art, and a commercially available compound library can also be used.

Please replace the paragraph on page 29, next to last line to page 30, line 6, with the following amended paragraph:

Since α_1 protease inhibitor and the extract formed a complex, a partial amino acid sequence of the extract from the complex was examined. Figure 4 shows the partial amino acid sequence of the factor IX-activating protein, which was obtained by the amino acid analysis. Databank analysis suggested that the protein was elastase. The molecular weight of the factor IX-activating protein of the present invention was approximately ~~29kDa~~ 25.7 kDa.

Please replace the last paragraph on page 30, lines 8-22, with the following amended paragraph:

Elution profiles of the enzyme peptides after fragmentation with different agents are shown in Figure 13. Cleaved fragments of the enzyme purified from erythrocytes are summarized in Table below. Although most masses of minor peaks were identified, but these are not listed in Table below. The deduced structure of the enzyme is shown

diagrammatically in Figure 14. The enzyme consisted of 219 amino acid residues ~~SEQ ID NO:4~~ (SEQ ID NO:4), and the molecular mass was 25.7 kDa (Table below). Sugar residues were estimated from a comparison of the measured masses of sugar-linked fragment and the theoretically predicted mass (Table 1). The difference was approximately 880 Da for fragment 75-115 and 135-154 which suggests that the sugar chains are likely GlcNac(Fuc)-GlcNac-Man-Man. Mass of the whole protein differed to the calculated mass by about 1,760, which is in accord with two N-linked carbohydrate chains.

Please replace the table on page 31, l with the following amended table:

Table 1

Determination of cleaved fragments of F-IX-activating enzyme

Fragment type	Fragment of SEQ. ID NO. 4	Peak number	Observed mass	Calculated Mass	Assigned sequence
Tryptic Fragments	1-6	1	659.08	657.79	IVGGRR
	7-21	6	1825.18	1810.18	ARPHAWPFMVSLQLR
				(1826.18)	(Methionine sulfoxide)
	22-49	5	2990.28	2974.42	GGHFCGATLI....AHCVANVNVR
				(2990.42)	(Methionine sulfoxide)
	53-62	2	1065.39	1066.25	VVLGAHNLSR
	63-74	3	1486.64	1487.70	REPTRQVFAVQR
	68-74	2	847.25	847.99	QVFAVQR
	75-115	10	5331.75	4450.04	IFENGYDPVN....QVAQLPAQGRR
				(5327.86)	(+N-linked glycan)
	116-132	7	1822.28	1804.15	LGNGVQCLAMGWGLLGR
				(1820.15)	(Methionine sulfoxide)
	135-154	9	3094.36	2217.41	GIASVLQELNVTVVTSLCRR
				(3094.41)	(+N-linked glycan)
	154-162	4	1105.54	1106.29	RSNVCTLVR
	165-191	8	2821.96	2822.19	QAGVCFGDSG....GLIHGIASFVR
	192-219	11	3059.34	3055.44	GGCASGLYPD....VNWIDSIIQR
BNPS-skatole Fragments	1-12	12	1376.61	1375.79	IVGGRRARPHAW
	13-127			13486.41	PFMVSLQLRG....NGVQCLAMGW
	128-212			10019.26	GLLGRNRGIA....FAPVAQFVNQ
	213-219	13	844.58	844.99	IDSIIQR
Whole protein	1-219		25673.27	23915.56 (25669.19)	IVGGRRARPH....VNWIDSIIQR (+N-linked glycans)

Each fragment except for 13-127 and 128-212 was confirmed by amino acid sequence analysis.

Please replace the header of the table on page 33, lines 8-9, with the following header:

Table [[1]] 2 The time of onset of coagulation of whole blood and RBCs/PFP in normal subjects, diabetics, and normal pregnant woman

Please replace the paragraph on page 37, lines 8-17, with the following amended paragraph:

10 µl of 1.5 µM synthetic substrate (Suc(OMe)-Ala-Ala-Pro-Val-MCA) (SEQ ID NO: 7) specific to the enzyme of the present invention (enzyme extracted in Example 1(1)) was added to 40 µl of blood sample on polypropylene plate, and the plate was covered with cover glass and incubated at room temperature for 30 minutes. The fluorescence from the sample was observed under a fluoromicroscope (Model AX70, Olympus) at λex=380nm and λem=460nm. The results are shown in Fig. 11. In Fig. 11, fluorescence is observed if a synthetic substrate is cut with an enzyme on erythrocyte membrane to release AMC.

Please replace the paragraph on page 38, lines 2-9, with the following amended paragraph:

Erythrocytes were mixed with HEPES buffer containing 22.5 nM synthetic substrate (Suc(OMe)-Ala-Ala-Pro-Val-MCA) (SEQ ID NO:7) (Hematocrit: 1.5%), and the mixture was incubated at 37°C for 30 minutes. After reaction, the mixture was fully stirred, and erythrocyte suspension was centrifuged. The resultant supernatant was diluted 20 times,

and the fluorescent intensity of the solution was measured(λex=380nm, λem=460nm). The results are shown below.

Please replace the paragraph on page 39, lines 20-25, with the following amended paragraph:

The content of F-IX-activating enzyme, erythroelastase (EE-IX), in erythrocyte membrane was estimated from a comparison of fluorescence intensity of a mixture of a fluorogenic synthetic substrate (Suc(OMe)-Ala-Ala-Pro-Val-MCA) (SEQ ID NO:7), Calbiochem-Nova Biochem), specific for elastase, with elastase and with erythrocytes.

Please replace the paragraph on page 40, lines 22-27, with the following amended paragraph:

Relative activity of the enzyme is a ratio of the fluorogenic intensity of the mixture of a fluorogenic synthetic substrate (Suc(OME)-Ala-Ala-Pro-Val-MCA) (SEQ ID NO:7), specific for elastase, the enzyme and inhibitor or antibody to that of the mixture of the fluorogenic substrate and enzyme not containing inhibitor or antibody (control).